Appendix B

Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of the AntiInfective Drugs Advisory Committee

April 26 and 27, 2001

Holiday Inn, The Ballrooms,
8120 Wisconsin Ave., Bethesda, MD 20879

Members Present

L. Barth Reller, M.D.
Alan S. Cross, M.D.
Joan P. Chesney, M.D.
Celia Christie-Samuels, M.D.
David E. Soper, M.D.
Gordon L. Archer, M.D.
Barbara E. Murray, M.D.
James E. Leggett, Jr., M.D.
Ellen R. Wald, M.D.
Steve Ebert, Pharm, D.

FDA Participants

Diane Murphy, M.D.
Janice Soreth, M.D.
Joyce Korvick, M.D.
David Ross, M.D.
Alma Davidson, M.D.
Edward Cox, M.D.
Douglas Shaffer, M.D.
George Rochester, Ph.D.

Guest Speakers (April 26 only)

Dave Battinelli, M.D.
David Bell, M.D.
Barry Davis, Ph.D.
Zachary D. Goodman, M.D.
Ralph Lazzara, M.D.
William M. Lee, M.D.
Arthur Moss, M.D.
Jeremy Ruskin, M.D.
Ciro Sumaya, M.D.

These summary minutes for the April 26 and 27, 2001 meetings of the AntiInfective Drugs Advisory Committee were approved on May 10, 2001.

I certify that I attended the April 26 and 27, 2001 meetings of the AntiInfective Drugs Advisory Committee and that these minutes accurately reflect what transpired.

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Thomas H. Perez, M.P.H., R.Ph.
Executive Secretary

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L. Barth Reller, M.D.
Chair

This report contains public information that has not been reviewed by the agency or AntiInfective Drugs Advisory Committee. The official summary minutes will be prepared, circulated, and certified as usual. Transcripts will be available in about 12 days. External requests should be submitted to the Freedom of Information office.

The AntiInfective Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research met on April 26 and 27, 2001 at the Holiday Inn, The Ballrooms, 8120 Wisconsin Ave., Bethesda, MD. 20879

The committee discussed new drug applications (NDA) 21-144 for Ketek ™ (telithromycin), Aventis Pharmaceuticals, Inc., for the treatment of bacterial respiratory infections.

The Committee had received a briefing document from the FDA and a background document from Aventis.

There were approximately 300 persons present at the meeting. The meeting was called to order at 8:00am by the Chair, Barth Reller, M.D. The Committee members and discussants introduced themselves. Thomas H. Perez, Executive Secretary of the AntiInfective Drugs Advisory Committee read the Meeting Statement. Dianne Murphy, M.D., Director, Office of Drug Evaluation IV, provided opening comments.

At approximately 8:30, Dr. Jeremy Ruskin started his presentation on “Drug-Induced QT Interval Prolongation and Torsades de Pointes”. Dr. Douglas Shaffer followed with a presentation on “Macrolide Antibiotics and Torsade de Pointes Postmarketing Analysis”.

Aventis’ presentation began at 9:40 and included the following topics and presenters:

Introduction - - - - - Mindell Seidlin, M.D.,Vice President, Clinical Development, AntiInfectives
Microbiology - - - - Andre Bryskier, M.D., Senior Director, Clinical Microbiology
Human Pharmacology - - - Vijay Bhargava, Ph.D., Senior Director, Drug Metabolism and Pharmacokinetics
Clinical Efficacy & Safety - - Bruno Leroy, M.D., Senior Director, Clinical Development, AntiInfectives
ECG Analysis - - - Claude Benedict, M.D., Senior Vice President, Preclinical and Early Clinical Development
Conclutions - - - - - Mindell Seidlin, M.D., Vice President, Clinical Development, AntiInfectives

FDA’s presentation began at 1:00 and included the following topics and presenters:

Clinical Efficacy - - - - - - - - - George Rochester, Ph.D., Senior Statistician, Division of Biometrics III
Resistant S. pneumoniae - - Alma Davidson, M.D., Medical Officer, Division of AntiInfective Drug Products
General *Safety Profile* - - - - David Ross, M.D., Ph.D., Team Leader, Division of AntiInfective Drug Products
Hepatic Effects - Edward Cox, M.D., Medical Officer, Div. of Special Pathogens & Immunologic Drug Products
Drug- Induced Liver Disease - - - Zachary D. Goodman, M.D., Armed Forces Institute of Pathology
FDA Presentation Summary - - - - David Ross, M.D.

The Open Public Hearing portion of the meeting had no participants.

The Committee began discussion of the questions and vote portion of the meeting at 4:00 with the following questions.

I. Given the risks of cardiac and hepatic toxicity of telithromycin, does the efficacy for telithromycin in respiratory infections support its use for:
   - community acquired pneumonia;

     Yes 7 *No 3*

   - acute exacerbation of chronic bronchitis;

     Yes 0 *No 10*

   - acute sinusitis?

     Yes 2 *No 8*

In your discussion please comment on the following:

A. Has the applicant provided sufficient data to warrant a claim for the treatment of community-acquired pneumonia due to penicillin-resistant *S. pneumoniae* (PRSP)?

   Yes 3 *No 7*

   - If NO, what additional studies should be conducted?

   Members of the Committee expressed a need for more studies and more patient information, particularly in treating bacteremic patients and also resistant organisms.

B. Is there sufficient evidence that an infection due to erythromycin-resistant *S. pneumoniae* (ERSP) has a negative impact on clinical outcome compared to that of sensitive strains of *S. pneumoniae*?
   - If YES, has the applicant provided sufficient data to warrant a claim for the treatment of community acquired pneumonia due to erythromycin-resistant *S. pneumoniae* (ERSP)?
   - Comment on the potential for concurrent-resistance of telithromycin and the macrolide antimicrobials?

   The Committee reworded the question as follows:
   Should the drug, if approved, have a specific indication to treat infections due to erythromycin-resistant S. pneumoniae.

   Yes 3 *No 7*

   The Committee additionally expressed the following points;
   The numbers of patients studied is small, particularly for patients with bacteremic pneumonia. They would like to see more data on cross resistance.

C. If the committee recommends approval, should this approval involve restrictions? For example, restrictions in the label use in special populations only, limitations in access or distribution.

The following issues were discussed in reference to community acquired pneumonia*:*
Concern for the emergence of telithromycin-resistant pneumococci during therapy
The Committee did not believe there are sufficient data on risk factors for toxicity currently to enable preparation of guidelines for safe use.
More data on safety from pre-marketing studies of older patients are needed to define drug interactions.
Additional pre-marketing studies are preferred to post-marketing surveillance alone to better assess safety.
Mandate large studies to better define C-max and AUC in the elderly, and to enumerate drug risks and side effects,particularly for hepatotoxicity.
Describe potential drug / drug interactions.
Drug should not be indicated for prolonged use.
Patient labeling should be provided as in a medication guide.
Use in patients not requiring hospitalization.
Risk groups should be noted to ensure caution is exercised.
Note the potential for prolongation of the QT interval.

II. If the committee has not recommended approval, please provide recommendations for additional studies if appropriate.

The Committee recommended that a drug safety profile be established to describe toxicity. Larger numbers of patients need to be enrolled to determine safety. In addition, patients with isolates of penicillin-resistant S. pneumoniae and H. influenzae should be targeted.

The meeting was adjourned at 5:30 p.m.

The meeting on Friday, April 27, 2001, was a closed meeting of the Committee.